

Mechanism of antihypertensive effect of thiazide diuretics

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The thiazide diuretics have become established as the drugs of first choice in the treatment of hypertension. Not only do they exert an independent antihypertensive effect but they also enhance the action of other antihypertensive drugs and prevent the development of resistance to various adrenergic blocking and vasodilator agents used for treating hypertensive patients.

The mechanism of the antihypertensive effect of the thiazides has not been clarified. Pharmacological textbooks^{1, 2} ascribe the antihypertensive action to two mechanisms as follows: (1) depletion of extracellular fluid volume (ECF) including plasma volume accounting for the initial fall of blood pressure, followed by (2) decreased peripheral vascular resistance due to a direct vasodilator action of the drug. It is generally believed that the vasodilator action contributes importantly to the long-term antihypertensive effect of these drugs.^{1, 2} The presently accepted theory of the antihypertensive action of the thiazides, therefore, defines two entirely separate mechanisms, a diuretic and a vasodilator action. Furthermore, they are said to act primarily in sequence rather than together. Such a dual theory, however, must be regarded with suspicion, because (1) it is unusual for any drug to exert its therapeutic effect via one mode of action initially and via an entirely different mechanism later on, and (2) a direct vasodilator effect of the thiazides has never been convincingly demonstrated.

In the present investigation the mode of action of the thiazides has again been investigated by recording both the short and long-term effects of hydrochlorothiazide. Among the hemodynamic parameters investigated are cardiac output, plasma volume, and ECF. Using these data as well as previous reports in the literature a unitary rather than the present dual theory of the mode of action of the thiazides will be presented.

Methods

Thirteen patients with essential hypertension of mild to moderate severity who were attending the Hypertension Clinic of the Veterans Administration Hospital consented to participate in the study after being fully informed of its design and purposes. The patients either were previously untreated or were receiving thiazide diuretics without other drug treatment. Prior to the control determinations, the latter patients were placed on placebos for a 2 to 3 week period. Pill counts were carried out throughout the trial as a test of compliance. One patient dropped out while another was noncompliant as judged by the pill counts. Both were dropped from the study.

The patients were studied on four occasions as follows: before treatment, 48 hours after beginning treatment with hydrochlorothiazide 50 mg. twice daily to determine acute effects of the drug, and 6 weeks as well as 8 weeks after beginning treatment with hydrochlorothiazide for assessing long-term effects.

During test days patients came to the laboratory in the fasting state. An 18 gauge Teflon catheter was inserted into an antecubital vein to facilitate blood sampling. Plasma volume and extracellular fluid measurements were determined in eight patients by the method of Gregersen and Stewart,³ adapted for use with the

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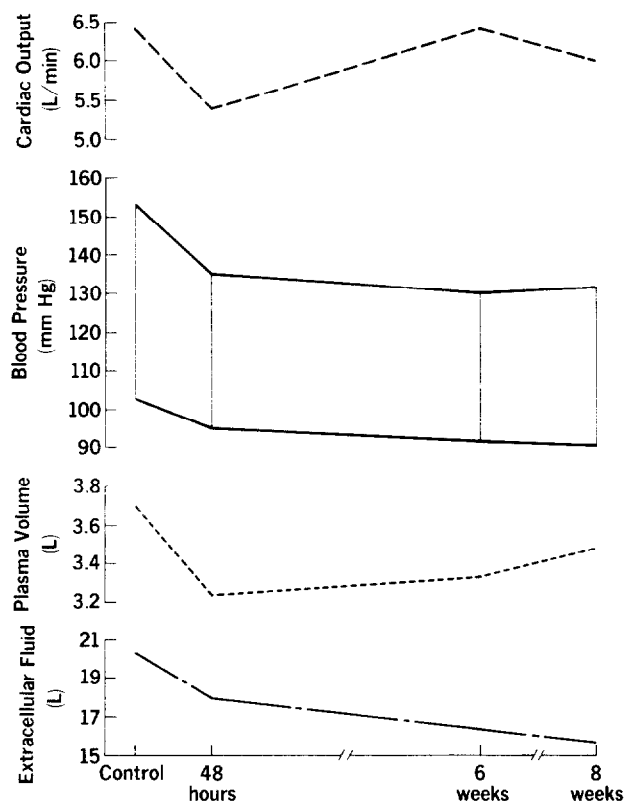


Fig. 1. Mean changes in cardiac output, blood pressure, plasma volume, and extracellular fluid volume (thiocyanate space) before as well as 48 hours, 6 weeks, and 8 weeks after treatment with hydrochlorothiazide.

spectrophotometer. The procedures were carried out after the patients had remained continuously in the recumbent position for at least 30 minutes. After drawing control samples of blood, 22.5 mg. of Evans Blue dye in 5 ml. of distilled water and 18 ml. of 5 per cent sodium thiocyanate were injected into an antecubital vein using calibrated syringes. Blood samples were drawn from a vein in the opposite arm for plasma volume determination at 10, 15, and 20 minutes after the injection of Evans Blue dye. The concentrations at these times were plotted on semilog paper and a best fit line was extrapolated back to zero time. The latter concentration was taken as the value present after mixing and before any disappearance of the dye.

Blood samples were drawn for thiocyanate determinations at 2 hours following injection as well as 10 minutes later. Thiocyanate concentration of the second sample was required to agree within 5 per cent of the first. The average concentration of these two samples corrected for the plasma blank was used to determine the

thiocyanate space.¹ While this method only approximates the true extracellular fluid volume since the thiocyanate ion enters red cells and other compartments, prior experience indicated that this method is reliable for measuring changes in the ECF.¹

Cardiac outputs were determined by the CO_2 rebreathing method alone in six patients and by the CO_2 rebreathing method and the dye dilution methods in five patients. Cardiac output was determined by the CO_2 rebreathing method before the administration of hydrochlorothiazide and 48 hours, 6 weeks, and 8 weeks after initiating treatment with the drug. After resting in the supine position for at least ten minutes the blood pressure was recorded by the same observer throughout, using the standard auscultatory method. The fifth phase of the Korotkoff sounds were used as the indication of diastolic blood pressure. The blood pressure was recorded before and after each determination of cardiac output and the results were averaged. The initial determinations of blood pressure and cardiac output were discarded in order to accustom the patient to the procedure prior to the collection of data. Cardiac output also was determined by the dye method in five of the patients before beginning treatment with hydrochlorothiazide and 8 weeks after beginning treatment. The significance of differences after as compared to before treatment was determined using Student's *t* test.

The technique of Franciosa and associates² was used for estimating cardiac output by the CO_2 rebreathing method. Their technique was modified slightly with respect to the point at which CO_2 is measured in the expired air. Rather than using forced expiration, which in our hands frequently lead to an overestimate of alveolar CO_2 , we recorded the CO_2 concentration in expired air during normal or deep respiration at a point where the expired volume approximated 400 ml. The CO_2 concentration and the respiratory volume were recorded continuously and simultaneously. The 400 ml. point was chosen because it well exceeded the dead space volume of 150 to 250 ml. but was not so large as to reflect the CO_2 concentration in underventilated alveoli such as we had experienced using forced expiration.

For the dye dilution method, a polyethylene catheter was inserted into an antecubital vein and was threaded into a central vein. A Teflon catheter was then inserted via a needle into the brachial artery. Mean arterial blood pressure was

Table I. Hemodynamic changes from control at 48 hours, 6 weeks, and 8 weeks after beginning treatment with hydrochlorothiazide

Parameter	No. of cases	Control	During treatment					
			48 Hours		6 Weeks		8 Weeks	
		Mean	Mean	P*	Mean	P*	Mean	P*
Body weight (lbs.)	11	201	197	<.005	197	<.05	196	<.01
Hematocrit (%)	11	40.4	43.1	<.005	42.6	<.0005	42.7	<.0005
Plasma volume (L.)	8	3.69	3.23	<.005	3.33	<.005	3.47	NS
Extracellular fluid volume (L.)	8	20.4	18.0	<.005	16.4	<.0005	15.4	<.005
Systolic blood pressure (mm. Hg)	11	153	135	<.01	130	<.01	131	<.005
Diastolic blood pressure (mm. Hg)	11	103	95	<.05	92	<.025	91	<.01
Heart rate (per min.)	11	76	79	NS	78	NS	77	NS
Cardiac output (L./min.)	11	6.4	5.4	<.025	6.4	NS	6.0	NS
Total peripheral resistance (Dynes cm. ⁻² /sec.)	11	1479	1716	.08	1356	NS	1393	NS

*Change from control using 1 tailed test.

Table II. Simultaneous determination of cardiac output by the Cardiogreen dye and CO₂ rebreathing methods

Patient No.	Control period				After 8 weeks of thiazide treatment			
	Cardiac output CO ₂ (L./min.)	Cardiac output Dye (L./min.)	Mean arterial pressure† (mm. Hg)	Total peripheral resistance (Dynes-cm. ⁻² /sec.*)	Cardiac output CO ₂ (L./min.)	Cardiac output Dye (L./min.)	Mean arterial pressure (mm. Hg)	Total peripheral resistance (Dynes-cm. ⁻² /sec.*)
6	7.85	6.83	115	1346	6.80	8.37	110	1294
8	7.39	6.37	151	1897	4.98	5.83	95	1303
9	8.06	6.71	113	1346	6.02	6.15	105	1482
10	5.21	4.90	133	2171	6.90	6.45	123	1525
11	7.02	7.19	92	1023	6.22	6.01	87	1158
Mean	7.11	6.40	121	1557	6.50	6.25	104	1352
S.D.	0.11	0.89	22	466	0.13	0.38	14	150

*Dye outputs used to calculate total peripheral resistance.

†Direct intra-arterial recording of blood pressure.

measured directly using a Statham strain gauge. After injecting rapidly 5 mg. Cardiogreen in one ml. distilled water into the central vein using a flush of 5 ml. saline, blood was withdrawn from the brachial artery through a Gilford densitometer using a motor-driven withdrawal syringe. The resulting dye-concentration curve was recorded on a Hewlett-Packard oscillographic recorder. Because of the more invasive nature of the procedure three such dye curves were recorded only during the control period and again at 8 weeks following initiation of treatment. It was not considered necessary to determine the acute effects of thiazides on cardiac output with the dye technique because such early effects as were determined by the dye dilution method have

already been well defined.¹⁰ The dye dilution method was used primarily to confirm the results obtained with the noninvasive CO₂ method on the effects of long-term treatment with the thiazides.

Results

Cardiac output, blood pressure, total peripheral resistance, and heart rate. Cardiac output as determined by the CO₂ rebreathing method fell significantly ($P < .05$) from a mean value of 6.4 L. per minute during the control period to 5.4 L. per minute 48 hours after beginning hydrochlorothiazide (Table I, Fig. 1). However, 6 and 8 weeks after beginning treatment with hydrochlorothiazide, cardiac output rose to or toward the

pretreatment values and was then insignificantly different from the pretreatment control level.

Cardiac output determined by the dye method in five patients agreed reasonably well with the cardiac output determined by the CO₂ rebreathing method (Table II). The correlation coefficient comparing both methods was $r = 0.84$ ($P < .05$) during the control period and $r = 0.97$ ($P < .005$) after 8 weeks of treatment. After 8 weeks the mean change in cardiac output from pretreatment control was -0.2 L. and -0.6 L. for the dye and CO₂ rebreathing methods, respectively. Neither change was significant.

By contrast to the initial fall and later return of cardiac output, the blood pressure fell early and remained reduced (Table I, Fig. 1). The average control blood pressure of 153/103 fell to 135/95 mm. Hg after 48 hours ($P < .05$). After 6 and 8 weeks of treatment the blood pressure was even lower, averaging 130/92 and 131/91 mm. Hg at 6 and 8 weeks, respectively ($P < .025$).

Total peripheral resistance increased initially from a mean of 1479 dynes-cm.²-sec. in the control period to 1716 dynes-cm.²-sec. 48 hours after beginning hydrochlorothiazide. The change was of borderline significance ($P = .09$). After 6 and 8 weeks, total peripheral resistance decreased slightly but not significantly below the control level, the mean values being 1356 and 1393 dynes cm.² per second respectively at the 6 and 8 week post-treatment periods.

Heart rate did not change significantly throughout the treatment period. The mean value for heart rate rose insignificantly from 76 per minute in the pretreatment period to 79 per minute at 48 hours after beginning treatment. The mean values for heart rate at 6 and 8 weeks after beginning treatment remained within the range of these values.

Extracellular fluid volume, plasma volume, hematocrit, and body weight. ECF measured in eight patients by the thiocyanate method fell significantly and remained reduced throughout the period of observation (Table I). From a mean control value of 20.4 L. the ECF decreased 12 per cent to 18.0 L. at 48 hours after beginning hydrochlorothiazide. The reductions in ECF were even greater at 6 and 8 weeks, averaging 20 and 24 per cent, respectively, below the control mean.

Plasma volume decreased from a mean of 3.69 L. in the control period to 3.23 L. 48 hours after beginning treatment with hydrochlorothiazide.

The decrease averaged 13 per cent and was highly significant ($P < .005$). Plasma volume remained reduced at 6 and 8 weeks after treatment with hydrochlorothiazides, although the change attained statistical significance only at the 6 weeks interval.

Reflecting the decrease in plasma volume the hematocrit rose and remained significantly above the control mean throughout the 8 week period of treatment. The mean value in the control period was 40.4 and this rose to 43.1 after 48 hours of treatment, an increase of 7 per cent. The mean values at 6 and 8 weeks of treatment were essentially the same as at 48 hours (Table I).

Body weights decreased at 48 hours after treatment and remained significantly below the control for the remainder of the period of observation. The average loss of weight was 4 pounds or 1.8 kilograms at 48 hours, increasing to 5 and 6 pounds (2.3 and 2.7 kilograms), respectively, at 6 and 8 weeks after beginning treatment.

Discussion

Three principal hypotheses have been advanced to explain the antihypertensive effects of the thiazide diuretics. The first two hypotheses are concerned with sodium depletion, of which one ascribes the fall in blood pressure to a reduction in total ECF and the other to a loss of sodium from the arterial walls. The latter hypothesis probably can be discarded, because studies from three independent sources found no evidence that thiazides affect the sodium content of either large or small arteries in rats.⁹⁻¹¹ The third and most popular hypothesis is that the hypotensive effect, at least during chronic treatment, is due to a direct vasodilator effect of these drugs.^{1, 2}

Hollander, Chobanian, and Wilkins¹² found no reduction in extracellular fluid volume after one to six months of treatment with chlorothiazide. On the basis of this and other data, they concluded that the antihypertensive effect was not due solely to sodium depletion. Their conclusion gained support from the observation that the chemically related compound, diazoxide,¹³ is a vasodilator antihypertensive compound which produces sodium retention rather than diuresis.^{14, 15} According to Rowe and colleagues,¹⁵ acute administration of diazoxide is associated with a considerable decrease in total peripheral resistance in hypertensive patients and with a

reflex increase in heart rate and cardiac output similar to that seen with other vasodilator drugs, such as hydralazine or amyl nitrite. Acute administration of the thiazides, however, is associated with the opposite hemodynamic effects, that is, with an increase in total peripheral resistance and a fall in cardiac output.⁷⁻⁹ Also the initial observation¹¹ that hypotension preceded the diuresis has not been confirmed, as three other investigations concluded that the fall in blood pressure occurred only after an effective diuresis.¹⁶⁻¹⁸ Furthermore, a direct vasodilator effect of the thiazide diuretics has not been convincingly demonstrated.

The vasodilator theory of the action of the thiazides has been further questioned by the observation that other diuretics, such as parenteral mercurials¹¹ and ethacrynic acid,¹⁹ also exhibit an antihypertensive effect. These drugs have in common volume depleting effects rather than vasodilator properties. Also, the reduction of blood pressure occurring in patients receiving the low-sodium "rice diet" is associated with a significant reduction in ECF.^{20, 21} All of the above antihypertensive procedures decrease ECF, suggesting that it is the latter which is causally implicated in the reduction of blood pressure in both the acute and chronic responses.

Volume depletion following acute administration of the thiazides has been documented by many investigators.^{4, 16, 22-26} Patients undergoing continuous treatment with thiazides lose about 2 L. of ECF and about 300 to 400 ml. of plasma volume during the first 72 hours of treatment. After this time there is no additional volume depletion. However, the reduction in ECF which occurs during the first 72 hours is maintained. Patients receiving diets severely restricted in sodium show quantitatively similar reductions averaging 10 per cent of the ECF and 15 per cent of the plasma volume.^{20, 21}

The importance of reduced volume is again indicated by observations that the antihypertensive effects of combined treatment with thiazide diuretics and adrenergic blocking agents can be reversed in many patients by re-expanding the plasma volume with salt-free dextran.^{16, 17, 15} However, in patients treated with thiazides without adrenergic blocking agents, dextran will only occasionally but not usually restore the hypertension.²¹ Nevertheless, oral ingestion of 20 to 30 Gm. salt, which is sufficient to re-expand

total ECF despite the administration of thiazides, does restore the hypertension even during long-term treatment.²²⁻²⁴ This suggests that re-expansion of total ECF rather than plasma volume alone is required to overcome completely the antihypertensive effects of the thiazides.

Three possible mechanisms can be postulated to explain how thiazide-induced reduction of ECF lowers blood pressure. Firstly, volume depletion may blunt environmental pressor stimuli while at the same time enhancing depressor influences. For example, patients receiving ganglion-blocking agents often exhibit marked hypotensive responses with only small reduction of blood volume.²⁷ It has further been observed that following either thiazide or mercurial-induced diuresis, the depressor responses to infused trimethaphan are increased.²⁸ Also, expansion of ECF in rats results in an enhanced pressor response to angiotensin whereas ECF depletion has the opposite effect.²⁹ Volume depletion, therefore, seems to dampen pressor reactions and increase depressor responses, the combined effects of which could result in a reduction of average blood pressure. While this theory is attractive, it does not explain the rise in cardiac output toward control values and fall in total peripheral resistance which occurs with long-term treatment.

The second possible mechanism by which volume depletion may lower blood pressure is via the baroreceptor reflexes. It has been noted clinically that elderly patients often exhibit an enhanced hypotensive response to the thiazide diuretics requiring reduction of dosage, often to quite small amounts. On the other hand, young normal adults do not show an antihypertensive effect with the thiazide diuretics, although their heart rates increase significantly consistent with an active baroreceptor response to the lower blood pressure associated with the volume depletion.²³ Elderly normal subjects, however, do show a fall of blood pressure with the thiazide diuretics.³⁰

Baroreceptor reflex responses depend upon the compliance of the aorta and carotid artery. These vessels become less distensible as a result of structural changes induced by aging or by hypertension. Homeostatic circulatory adjustment to pressor stimuli are poorly moderated in longstanding chronic hypertension.³¹ While the evidence is incomplete, it is consistent with the

concept that the antihypertensive effect of the thiazide diuretics, at least in patients with noncompliant arteries, could be due in part to an inadequate baroreceptor compensation for the volume depletion and reduced cardiac output.

The third, and we believe most likely mechanism, for explaining the hemodynamic changes seen with the thiazide diuretics involves feedback autoregulatory responses to a prolonged reduction in cardiac output as originally suggested by Tobian.^{32, 33} Such feedback autoregulatory systems have been postulated to explain the rise of blood pressure which occurs in certain types of experimental hypertension. In experimental renovascular hypertension³⁴ or in the hypertension caused by reduction in renal mass plus salt loading,³⁵ or in the hypertension induced by excess licorice ingestion in man,³⁶ the following sequence of events was observed during the development of the hypertension: (1) salt and water retention, leading to (2) expansion of the ECF and plasma volume, resulting in (3) increased venous pressure and venous return to the heart, followed by (4) increased cardiac output, (5) rise in blood pressure, leading to (6) increase in urine volume preventing further rise in ECF, followed by (7) gradual elevation of total peripheral vascular resistance occurring over a period of weeks. It was postulated that the rise in total peripheral resistance was due to autoregulation in response to the elevated peripheral blood flows which were in excess of local metabolic needs because of the increased cardiac output. At the same time, there was (8) reduction of the elevated cardiac output toward normal because of the elevated afterload resulting from the increase in total peripheral resistance. Thus, the hypertension which was initiated by an expansion of ECF and resulting increase in cardiac output evolved after approximately one month into a hypertension characterized by an elevated total peripheral resistance and normal cardiac output.

Tobian^{32, 33} has postulated that thiazides and related diuretics induce "reverse autoregulation" which leads to a decrease in total peripheral resistance. Thus, reduction in ECF caused by thiazides produce initially a fall in central venous pressure, venous return, and cardiac output. At first, this is associated with an increased total peripheral resistance. However, with continued treatment and maintained reduction in cardiac output and total blood flow, autoregulation

occurs gradually over a period of weeks leading to a decline in total peripheral resistance. Finally, we suggest that the resulting fall in afterload permits a rise in cardiac output toward normal. This sequence of hemodynamic events is the same as that actually observed during the early and late phases of continuous treatment with the thiazides, and they all follow from a single hemodynamic effect of the thiazides which is a sustained reduction in ECF. No direct vasodilator action of the thiazides need to be postulated, as the early fall and later return of cardiac output to normal and the early rise and later fall in total peripheral resistance can both be explained by the reduction in ECF alone.

Most pharmacological textbooks differentiate between the short-term and long-term effects of thiazides.¹⁻³ According to these texts the short-term antihypertensive effect is due primarily to volume depletion while the long-term effect is ascribed to a vasodilator action of the thiazides. The principal evidence for such a dual mechanism of action is the report of Conway and Lauwers,³⁷ which indicates that plasma volume and ECF fall initially but then return to essentially control values after one month of continuous treatment with chlorothiazide. These investigators concluded that decreased ECF could not have an influence on the long-term antihypertensive effect of the thiazides.

Other investigators, however, have not corroborated the observations of Conway and Lauwers. Wilson and Freis¹ found a significant reduction of ECF after six months of continuous treatment with chlorothiazide. Plasma volume also was reduced at six months, although not significantly. However, at 12 months plasma volume was significantly lower than control. More recently, other investigators also found a continued reduction of plasma volume and ECF during long-term treatment with thiazides.³⁸⁻³⁹ Furthermore, following withdrawal of long-term treatment there was a prompt and significant rise of plasma volume, ECF, and blood pressure, providing further evidence that the thiazides continue to maintain their volume-reducing effect during chronic administration.^{1, 38}

Conway and Lauwers³⁷ also observed that while cardiac output falls initially after administration of thiazide, it returns to normal after one month. The latter observation has been confirmed in the present study and by Lund-Johan-

sen.¹⁰ During the first few days of treatment, cardiac output is reduced and total peripheral resistance is increased.^{6,8} However, after a month or more of treatment, cardiac output rises to or toward control values while total peripheral resistance falls. These changes can be explained by reverse autoregulation without invoking a separate vasodilator effect of the thiazide diuretics.

Autoregulation may not be limited to the thiazides alone. Other antihypertensive agents also induce differing hemodynamic effects during acute and chronic administration. Guanethidine, an adrenergic blocking agent, causes an initial fall in cardiac output but with long-term treatment cardiac output rises gradually back toward normal.¹¹ Hydralazine, a vasodilator agent, initially increases cardiac output but the latter returns toward normal during chronic treatment.¹² These observations suggest that autoregulatory responses which return the cardiac output toward normal often occur during long-term administration of antihypertensive agents.

Summary

Hemodynamic studies were carried out before and during 8 weeks of treatment with hydrochlorothiazide 50 mg. twice daily in 11 hypertensive patients. Forty-eight hours after beginning treatment there was a significant reduction in blood pressure, cardiac output, plasma volume, and extracellular fluid volume (thiocyanate space) while total peripheral resistance increased. After 6 and 8 weeks of treatment, the blood pressure and the plasma and extracellular volumes remained reduced. However, total peripheral resistance fell while cardiac output rose to control levels. These results were consistent with the "reverse autoregulation" theory of the action of the thiazides as proposed by Tobian. The present findings as well as other clinical and experimental evidence discussed below makes it appear unlikely that the thiazides have an important direct vasodilator effect.

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